UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/996,954	11/30/2001	Harlan W. Waksal	1017.33537A.US3	3116

20311 7590 11/02/2007

LUCAS & MERCANTI, LLP
475 PARK AVENUE SOUTH
15TH FLOOR
NEW YORK, NY 10016

EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	**PAPER NUMBER**
1643	
MAIL DATE	**DELIVERY MODE**
11/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/996,954	WAKSAL, HARLAN W.	
	Examiner	Art Unit	
	Anne L. Holleran	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-87 and 89-98* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-87 and 89-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This Office action supersedes the Office action mailed out 5/15/2007, which is hereby VACATED.

2. The amendment filed 2/15/2007 is acknowledged. Claim 88 was canceled. Claims 71-87 and 89-98 are pending and examined on the merits.

Claim Rejections Withdrawn:

3. The rejections of claims 88 and 91 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims.

4. The rejection of claims 86-89 under 35 U.S.C. 112, first paragraph, for the reason that the specification, while being enabling for humanized antibodies that comprise all six CDRs of parent antibody such as the C225 chimeric antibody (which clearly has tumor growth inhibitory activity), does not reasonably provide enablement for humanized antibodies where the humanized antibody does not contain all six of CDRs of the parent antibody, or contains CDRs that are altered from the CDRs of the parent antibody, is withdrawn in view of the amendments to the claims.

5. The rejection of claims 71, 72, 76-87, 90, 92-94, 96 and 97 under 35 U.S.C. 103(a) as being unpatentable over Ciardiello (Ciardiello, F. et al, Journal of the National Cancer Institute, 88(23): 1770-1776, 1996) in view of Bos (Bos, M. et al., Proceedings of the American Society of Clinical Oncology, Abstract #1381, 1996) is withdrawn in view of applicant's persuasive arguments that the GEO xenograft model is not a model of a drug resistant tumor or of a refractory tumor, and that the observed lack of sensitivity to 8-Cl-cAMP was dose dependent.

6. The provisional rejection of claims 71-98 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 34-56 and 72-87 of copending Application No. 11/018,950 is withdrawn upon further consideration, because the claims of copending application 11/018,950 are drawn to methods comprising the administration of an EGFR antagonist in combination with a chemotherapeutic agent, which is an invention that is excluded by the claims of the instant application.

Claim Rejections Maintained:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 71-87, 90, 92, 96 and 98 remain rejected under 35 U.S.C. 102(b) as being anticipated by Bos (Bos, M. et al., Proceedings of the American Society of Clinical Oncology,

Abstract #1381, 1996) as evidenced by Herbst (Herbst, R.S. et al, Expert Opin. Biol. Ther. (2001) 1(4): 719-732) for the reasons of record.

Applicant's arguments have been carefully considered but fail to persuade. Applicant argues that in order for a reference to anticipate a claim, each and every element of the claim must be disclosed in that one reference. Applicant states that the pending claims are directed to methods for treating refractory tumors that have failed or been resistant to treatment with chemotherapy or radiation therapy. Applicant asserts that because Bos does not explicitly teach "refractory tumors" but instead refers to treating "advanced cancers" that the claims are not anticipated by Bos. Applicant also provides the Rowinsky Declaration filed under 37 CFR 1.132, by Eric Rowinsky. In the Rowinsky Declaration, the statement is made that advanced cancer is a stage of cancer in which the disease has either spread from the primary site to other parts of the body, directly or by traveling through the network of lymph glands (lymphatics) or in the bloodstream, or remains at the primary site but, for several reasons, including extensive size and/or tissue invasion, is not readily treated by local therapy (resection) performed for curative intent. A patient with an advanced cancer may be treated with chemotherapy or radiation therapy, and the advanced cancer might at some future date become refractory to such treatment. Applicant asserts that because Bos fails to disclose that the advanced cancer patients had previously been treated and had become refractory to the treatment that Bos fails to teach a method of treating refractory tumors with an anti-EGFR antibody. The purpose of the Rowinsky Declaration appears to be to draw a distinction between "advanced cancer" and "refractory cancer" and to suggest that someone with "advanced cancer" is not the same as someone with "refractory cancer". However, there does not appear to be a clear distinction between the terms

so that one of skill in the art would immediately understand that there is a dichotomy between advanced cancer and refractory cancer. The American Cancer Society defines advanced cancer as a cancer that usually cannot be cured, and that some people develop advanced cancer after years of treatment (see copy of website page http://www.cancer.org/docroot/CRI/content/CRI_2_4_1x What Is_Advanced_Cancer.asp?site area=).

Applicant's arguments fail to persuade because the Rowinsky declaration and the supporting arguments provided in the remarks that accompany the amendment or 2/15/2007 are concerned with the dictionary definitions of "advanced cancer" and "refractory cancer", but fail to provide any evidence that the patients that were treated in Bos were in fact patients that were treatment naïve, or were patients that were undergoing successful treatment. Because the use of an anti-EGFR antibody in human patients appears to have been a relatively new treatment at the time of publication of Bos, it is not plausible to the examiner that the patients treated in Bos were undergoing successful treatment. If the patients were treatment naïve, this would indicate that at around the time of the publication of Bos, there was no treatment strategy at all for any of the advanced cancers that were treated in Bos. However, the following references provide evidence that treatment options did exist for many of the cancers treated by Bos.

Lilenbaum, R.C. Curr. Opin. Pulm. Med., 2(4): 285-289, 1996; abstract only

Midthun, D.E and Jett, J.R., Postgrad. Med. 101(3): 187-188, 191-192, 194 passim., 1997; abstract only

Konety, B.R. and Getzenberg, R.H., Semin. Urol. Oncol., 15(1): 33-42, 1997; abstract only

Vokes, E.E. and Athanasiadis, I., Annals of Oncology, 7: 15-29, 1996

Canobbio, L., et al., Cancer Treat. Rev. 22(2): 85-104, 1996; abstract only

Regine, W.F. et al, Drugs Aging, 11(4): 285-295, 1997; abstract only

Lilenbaum teaches that chemotherapy has produced only modest survival benefits in patients with advanced non-small cell lung cancer. Midthun teaches that the treatment of advanced lung cancer (stage IV) with chemotherapy in combination with radiation produces a major response rate of 10%-30%. Konety teaches that in approximately a third of patients diagnosed with prostate cancer that responses to the standard therapy of androgen ablation are short-lived with progress of hormone refractory disease being inevitable. Vokes teaches that patients with head and neck cancer are treated with surgical resection and/or conventional radiotherapy with chemotherapy for patients with recurrent or metastatic disease. Vokes goes on to teach that a complex pattern of competing risks threatens the long-term survival of the head and neck cancer patient, with local and regional failure being the main challenge of the majority of patients (see page 15, first column). Canobbio teaches that among the treatments investigated for metastatic renal cell carcinoma, many oncologists consider the treatment of choice to be treatment with interferons or interleukin-2. However, of patients treated with alpha-interferon, 15-20% achieve an objective remission and 3-5% achieve a long-lasting complete response. Regine teaches that in pancreatic cancer patients with unresectable or locally advanced disease, combined modality therapy had produced the best results, but that only modest improvements in median survival and minimal increases in long term survival have so far been achieved.

The references cited above (Lilenbaum, Midthun, Konety, Vokes, Canobbio and Regine) have been discussed for the purpose of demonstrating that at around the time of the publication

of Bos, there appear to have been treatment strategies available for the treatment of several types of advanced cancers, and also to show that despite these treatments there was a greater than 50% chance that treatment would fail. Bos teaches a method of treating patients with advanced cancer and Herbst is cited to support the contention that at least one of the cancers treated in Bos (head and neck cancer) was a cancer that was a refractory cancer because Herbst teaches that fewer than 30% of patients will be cured. Applicant has argued that because Bos fails to explicitly teach treatment of refractory tumors, but instead discusses "advanced cancer", that Bos fails to anticipate the claimed methods. Thus, applicant appears to be suggesting that all of the patients in Bos were advanced cancer patients that had not been treated for their cancer (were treatment naïve), possibly due to the fact that there was no treatment available. This argument is not persuasive because almost all of the cancers that were treated in Bos were cancers for which available treatment modalities existed at around the time of publication of Bos, and also because it appears that advanced cancer may develop despite years of treatment. Because these cancers were also cancers that have a high failure rate, it appears that the "advanced cancer" patients of Bos were also patients that had refractory cancer.

The original rejection is included below:

Bos teaches a method of treating human patients having advanced cancer (with advanced cancer of the head and neck, prostate, lung, esophagus, pancreas and kidney), which is interpreted to read on refractory cancer, with C225 antibody, a chimeric monoclonal antibody that binds to EGFR. Additionally, some of the cancer patients treated in Bos' methods are patients with advanced head and neck cancer, which is a cancer that is taught by Herbst to be a refractory cancer (see page 719, "fewer than 30% of [...] patients will be cured"). Bos teaches

doses such as 100 mg/m^2, and teaches that two patients with head and neck cancer had minor responses, which is interpreted as indicating that there was some small degree of tumor growth inhibition. Additionally, the multiple dose study resulted in 5 patients completing 12 weeks of treatment without disease progression, which indicates that growth of the tumor was inhibited. Thus, Bos teaches methods that are the same as that claimed.

New Grounds of Rejection:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 71-87 and 89-98 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 71, 97 and 98 are indefinite because of the phrase "retains the ability to bind to the EGFR". The binding ability of what? If "the ability to bind" is that of any antibody fragment, then the ability to bind to EGFR may be minimal if the fragment is not an EGFR binding fragment. This would be obviated by amending the claims to positively recite that the fragment binds to EGFR.

Claim 80 is indefinite because of the phrase "binds EGFR externally". External to what? There is no description or definition provided in the specification.

Claims 84 and 86 are indefinite because of the phrase "further comprising". Because these claims do not set forth what the chimeric antibodies comprise in the first place, it is not

clear what they comprise. This rejection would be obviated by amending the claims to delete the word "further".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 91 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the specification fails to describe the genus of compounds that is encompassed by the functional term "immune system stimulator".

Claim 91 is drawn to a method comprising the treatment of patients with refractory tumors that have failed or been resistant to treatment with chemotherapy or radiation therapy comprising administering to a human without concomitant chemotherapy or radiation therapy, an epidermal growth factor receptor antagonist that is an anti-EGFR antibody or fragment thereof that retains the ability to bind to the EGFR, wherein administration is effective to inhibit growth of the refractory tumor, and further comprising administering an adjuvant that is an immune system stimulator.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was

in possession *of the invention*. The invention is for purposes of the 'written description' inquiry, "*whatever is now claimed*" (see page 1117). The specification does not exemplify or provide any examples of immune system stimulators that would be effective in the claimed methods, or provide any reasoning based on a structural analysis demonstrating a common structural feature for how to pick an "immune system stimulator" that would be effective in the claimed methods.

The skilled artisan cannot envision the detailed chemical structure of the encompassed "immune system stimulators" used in the method claims and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of manufacturing or testing the claimed process. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for making or testing it. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112, is severable from its enablement provision. (See page 1115).

9. Claim 80 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis of this rejection is that the amendment to the claims introducing the concept of an EGFR

antagonist that binds EGFR externally introduced new matter into the specification as originally filed.

Claim 80 is not an originally filed claim. The amendment that introduced claim 80 failed to indicate where in the specification support may be found for claim 80, and specifically for the concept of a method comprising the administration of an antibody that binds EGFR externally. As explained above, this phrase is indefinite because it is not clear what is meant by the phrase "binds EGFR externally". Furthermore, there does not appear to be any support in the specification for concept of external EGFR binding by an antibody, either explicit or implicit. Therefore, one of skill in the art would not find that applicant was in possession of methods comprising the administration of an EGFR antibody that binds EGFR externally.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claims 71 and 89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bos as evidenced by Herbst (supra) in view of Surani (US 5,545,807; issued Aug. 13, 1996).

Claims 71 and 89 include within their scope methods comprising the administration of an anti-EGFR antibody that is a human antibody. Bos as evidenced by Herbst teaches as set forth above, and teaches the use of a chimeric anti-EGFR antibody. Bos fails to teach the use of a human antibody that binds EGFR. However, methods for making human antibodies are known in the art as evidenced by the teachings of Surani, which teaches the use of transgenic animals to make human antibodies. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of Surani to create a human antibody that binds to EGFR for the purpose of treating the patients of Bos. One would have been motivated to use a human antibody, because a human antibody will be less immunogenic than will an antibody from another species (such as a mouse) or even compared to a chimeric antibody, which contains human sequences and mouse sequences.

11. Claims 71 and 93-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bos as evidenced by Herbst (supra) in view of Ladner (US 5,260,203; issued Nov. 9, 1993).

Claims 71 and 93-95 include within their scope methods comprising the administration of an anti-EGFR antibody that is a single chain antibody. Bos as evidenced by Herbst teaches as set forth above, and teaches the use of a chimeric (human/mouse) anti-EGFR antibody. Bos fails to teach the use of an antibody fragment that is a single chain antibody that binds EGFR. However, methods for making antibody fragments that are single chain antibodies are known in the art as evidenced by the teachings of Ladner. Further, Ladner teaches the advantages of single chain

antibodies over conventional antibodies are smaller size, greater stability and significantly reduced cost (see column 3, lines 32-37). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of Ladner to make a single chain antibody that binds to EGFR for the purpose of treating the patients of Bos. One would have been motivated to use single chain antibodies, because of the advantages of single chain antibodies as taught by Ladner.

12. Claims 71 and 97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bos (Bos, M. et al., Proceedings of the American Society of Clinical Oncology, Abstract #1381, 1996) in view of Malecka-Panas (Malecka-Panas, E. et al. Hepato-Gastoenterology, 44: 435-440, 1997) and Radinsky (Radinsky, R., European Journal of Cancer, 31A(7/8): 1091-1095, 1995).

Within the scope of claim 71 and specifically for claim 97, are methods of treating patients having refractory colon cancer.

Bos teaches a method of treating human patients having advanced cancer (with advanced cancer of the head and neck, prostate, lung, esophagus, pancreas and kidney), which is interpreted to read on refractory cancer, with C225 antibody, a chimeric monoclonal antibody that binds to EGFR. Bos teaches doses such as 100 mg/m^2, and teaches that two patients with head and neck cancer had minor responses, which is interpreted as indicating that there was some small degree of tumor growth inhibition. Additionally, the multiple dose study resulted in 5 patients completing 12 weeks of treatment without disease progression, which indicates that

growth of the tumor was inhibited. Bos fails to teach treating patients having a refractory tumor of the colon.

However, Malecka-Panas teaches EGFR is increased in patients with colon cancer (see abstract) and that the data of Malecka-Panas supports the hypothesis that EGFR receptor antagonists may be useful therapeutic agents in conditions characterized by increased proliferation of colon epithelium. Additionally, Radinsky teaches that expression of EGFR by human colon carcinoma cells (hCC) directly correlates with the ability of these cells to produce hepatic metastases (page 1093, 1st t0 2nd column, bridging paragraph and 2nd column). Radinsky also suggests that EGFR plays a role in the progression and metastasis of human colon carcinoma and suggest the use of EGFR antibodies as a potential treatment (page 1094) colon cancer. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the method of Bos to treat a patient with refractory colon cancer with the anti-EGFR antibody of Bos, because Bos demonstrates that administration of an anti-EGFR antibody results in the inhibition of growth of tumors in patients with advanced cancer and because the teachings of Malecka-Panas and Radinsky point to a correlation between EGFR status and proliferation characteristics of human colon cancer cells and advanced, metastatic human colon cancer cells. Therefore, one would have had a reasonable expectation of success in using the method of Bos to treat patients with refractory colon cancer because the EGFR had been identified in the prior art as a likely target for the treatment of colon cancer, and because the breadth of the claims encompasses treatment that results merely in temporary growth reduction of the refractory colon cancer.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
October 31, 2007

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER